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SOMATOSTATIN ANALOG TREATMENT OF PITUITARY TUMORS

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The recent clinical introduction of the Somatostatin analog SMS 201-995 (Sandostatin) provided the opportunity to study its effects on hormone secretion by and growth of pituitary tumors. In patients with growth hormone (GH)-secreting tumors 50 µg of SMS subc. normalized plasma GH levels for 2-6 hrs in 16 of 23 patients. Long-term therapy with 200-300 µg SMS daily in 2-3 injections resulted in normalization of mean plasma GH and Somatomedin-C (SM-C) levels in 5 out of 8 patients, and in suppression by 50-70% in the other patients. In parallel a striking clinical improvement was noticed in all patients. Tumor shrinkage occurred in 3 out of 6 patients. Apart from steatorrhea in 2 and deterioration of carbohydrate tolerance in 2 patients, no side-effects were observed during therapy for 8-78 weeks. No tachyphylaxis of pathological GH or normal insulin release was observed during long-term SMS therapy.
The mechanism of the inhibitory effect on tumor growth was investigated in the model of the PRL/ACTH secreting rat pituitary tumor 7315a. SMS 201-995 (2x6 or 2x20 µg daily for 30 days) inhibited tumor growth by 36 and 48%, resp. The tumor growth-inhibitory effect occurred during the first 15 days only. At the end of SMS treatment, tachyphylaxis of the GH-inhibitory effect had developed, plasma GH and SM-C levels of control and SMS-treated tumor rats being similar. In addition, the high corticosterone levels of the PRL/ACTH-secreting tumor-bearing rats interfered with the direct action of SMS on the pituitary tumor. This was shown in studies on the effects of SMS and dexamethasone on hormone release by cultured 7315a tumor cells.
In conclusion: chronic therapy with SMS 201-995 of patients with acromegaly was successful with regard to the inhibitory effects on GH and SM-C secretion, tumor size and the clinical picture. No tachyphylaxis developed during chronic therapy. In the rat, however, tachyphylaxis to the GH and SM-C lowering effect of SMS 201-995 developed rapidly.

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SOMATOSTATIN ANALOGUE TREATMENT OF APUDOMAS AND PANCREATIC TUMOURS

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Somatostatin is a natural inhibitor of hormone release produced both in the hypothalamus and in the D cells of the gastrointestinal mucosa and Islets of Langerhans. It appears to act mainly as a local (paracrine) hormone but is also found in low concentrations in the circulation. It was early found to inhibit growth hormone release from pituitary tumours, peptide release from the various pancreatic endocrine tumour types and also reduce the symptoms of the carcinoid syndrome and medullary carcinoma of the thyroid. Attempts to produce an analogue which affected only particular hormone systems in man, have been unsuccessful but recently an octapeptide has been developed by Sandoz Ltd (SMS 201-995) which extends the half clearance time of natural somatostatin (minutes) to hours and so makes subcutaneous therapy feasible. Thus 100 µg subcutaneously eight-hourly produces effective twenty-four hour suppression of hormone release. In a series of nine acromegalic patients treated for three months or more, there was significant suppression of growth hormone and IGF1 (though not to normal) and considerable amelioration of signs and symptoms. No significant tumour shrinkage occurred. The treatment was well received by the patient with no relevant side-effects (no rise in fasting glucose) occurred). In a series of pancreatic apudomas treated up to two and a half years the effects were found to be most beneficial in patients with VIPomas. In several cases end stage patients were treated who were otherwise unable to leave hospital. In three cases apparently pre-terminal patients returned to work and effectively normal health. Thus the somatostatin analogue 201 995 appears to be a significant addition to the therapy of endocrine tumours.

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EFFECTS OF SOMATOSTATIN ANALOG (SMS-A) TREATMENT (SANDOSTATIN) IN EXPERIMENTAL AND HUMAN CANCER.

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Effects of SMS-A treatment were investigated in different experimental tumor models. 1) In rats with transplantable pancreatic tumors we found ±35% inhibition of tumor growth after treatment with 5 doses SMS-A (0.05, 0.2, 1.0, 5.0, 10µg twice daily) during 6-9 weeks. Rats treated right from time of tumor inoculation showed pronounced inhibition of tumor growth after 2 weeks (4.1. ± 6.6 $mm^2$ (SD) vs. 45.8 ± 34.4 $m^2$ in controls) and 55% inhibition after 6-9 weeks. In tumor bearing rats body weight, plasma GH, IGF-1 and EGF were lower than in supercontrols without tumors. We observed slight suppressive effects of SMS-A on GH, IGF-1 and EGF in comparison to controls with tumors. Tumors incubated with $^{125}$I-SMS-A showed specific binding by autoradiography (J.C.Reubi, Sandoz, Basel). 2) No anti-tumor effects in rats with rhabdomyosarcomas. 3) In rats with DMBA induced mammary tumors maximal inhibition of tumor growth (83%) was reached with 2x0.2 µg/day; lower and higher doses of SMS-A appeared less or not effective. 4) Maximal inhibition (88%) of breast tumor cell growth (MCF-7) in vitro was obtained at a sharply defined dose of SMS-A ($10^{-8}$M) with a bell-shape dose-response curve. We found specific binding sites ($3x10^4$ molecules of 125I-SMS-A per cell). In a preliminary clinical study plasma IGF-1 was suppressed in >80% of 17 pat. with gastrointest. tumors treated with 3x200 µg/s.c./day. Anti-tumor effects: stable disease (3-9 months) in 3 pat. with metast. colorectalca.; no effect in 7 pat. with pancreasca. Side effect: increased fecal fat loss.
In conclusion: SMS-A showed clearly anti-tumor effects in some experimental models while the clinical data are too scarce for definite conclusions. More studies are needed to define the optimal dose and mode of administration. (Supported by grant RRTI 85-15 of the Netherlands Cancer Foundation)

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THE HYPOTHESIS OF HORMONAL MANIPULATION OF TUMOR CELLS IN COMBINATION WITH CHEMOTHERAPY

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Results of treatment for most advanced solid tumors are suboptimal and evaluation of new treatment strategies is needed. The endocrine dependence of human breast and prostate cancer has led to the development of studies of combined chemoendocrine therapy. Unfortunately these studies have been disappointing with no increase in response or survival with combined therapy. Studies using experimental models of human breast cancer have made the following observations: (1) antiestrogen therapy reduces cell proliferation, causes accumulation of cells in $G_1$ phase, and antagonizes the activity of several cytotoxic drugs; (2) estrogen replenishment restores cell proliferation, causes a synchronous wave of cells to leave $G_1$ phase and progress through the cell cycle, theoretically increasing their sensitivity to cycle active drugs. The ability to synchronize human breast cancer cells in experimental models has led to the development of clinical trials to test this hypothesis in patients with advanced breast and prostate cancers. Although preliminary results of some of these trials are encouraging, several questions remain to be answered. (1) Is synchronization and more importantly recruitment of $G_0$ $G_1$ cells possible with hormonal manipulation in patients? (2) What is the optimal dose and timing of the hormone treatment? (3) Does the timing of the cell kinetic alterations vary among patients? (4) What is the toxicity of this approach? (5) Is efficacy of cytotoxic chemotherapy increased by this strategy. The identification of growth factors involved in regulating proliferation of other tumor types may make this approach more widely applicable in the treatment of cancer.